REMARKS

Applicants have amended claims 1, 3, 10, and 11. Claims 1-3 and 5-11 are now pending in this application. The amended claims find support in the claims as originally filed and throughout the specification, and thus no new matter has been added.

Specification

The Office objected to the Specification because it "contains Figures 1-4 but does not contain a Brief Description of the Drawings." Office Action at page 2. Applicants note that the descriptions of Figures 1-4 are located on pages 12-13 of the Specification. The heading above these descriptions, "Legend to Fig. 1 to Fig. 4," has been deleted and replaced with the heading "Brief Description of the Drawings." Applicants therefore respectfully request that this objection be withdrawn.

Claim Objection

The Office objected to claim 11 because "the claim refers to HEL cells." Office Action at page 2. Applicants have amended claim 11 to recite the full name of the cell line as suggested by the Examiner. Accordingly, Applicants respectfully request that the objection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

The Office rejected claim 10 under 35 U.S.C. § 112, first paragraph, because platelets are cytoplasmic fragments of megakaryocytes and thus, are not considered

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hematopoietic cells. Office Action at page 3. Applicants respectfully traverse. To expedite prosecution, however, Applicants have amended claim 10 as the Examiner suggested, by deleting the term "platelets" and replacing it with the term "megakaryocytes." Applicants respectfully request the rejection be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The Office has also rejected claims 1-3 and 5-11 under 35 U.S.C. § 112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action at page 3. The Office stated that claims 1-3 and 5-11 are "indefinite as to whether the claimed modified FVIII cDNA contains only an intron and promoter or whether it is a factor VIII cDNA containing an inserted intron and a promoter." Office Action at page 3. Applicants respectfully traverse. To expedite prosecution, however, Applicants have added the element "wild type factor VIII cDNA" to claim 1. From this amendment it should be clear that Applicants are claiming a modified Factor VIII cDNA, not only an intron and a promoter. Applicants therefore respectfully request the rejection be withdrawn.

The Office also rejected claim 3, stating that it was "unclear as to the identity of the intron." Office Action at page 4. Applicants traverse. However, to expedite prosecution, Applicants have amended the phrase "truncated factor IX intron 1" to read "factor IX truncated intron 1." Because it is clear that the intron is truncated, Applicants respectfully request that the rejection be withdrawn.

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Finally, the Office rejected claim 10 as "indefinite for the limitation 'wherein said hematopoietic cells are platelets'." Office Action at page 4. Applicants traverse, however, based on the amendment of claim 10, it is respectfully requested that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Office has rejected claims 1-3 and 5-9 under 35 U.S.C. § 103(a) as "being unpatentable over Connelly *et al.* (Human Gene Therapy (1996) 7:183-195; referenced in IDS of Paper No. 6) and Negrier *et al.* (EP 1 048 726, 11-02-00; referenced in IDS of Paper No. 5), in view of Uzan *et al.* (J. Biol. Chem. (1991) 266(14): 8932-8939; referenced in IDS of Paper No. 4), Hoeben *et al.* (Thrombosis and Haemostasis (1992) 67(3): 341-345; referenced in IDS of Paper No. 5), and Hao *et al.* (Human Gene Therapy (July 1995) 6: 873-880)." Office Action at page 5. Further, the Office has rejected claim 11 under 35 U.S.C. § 103(a) as being "unpatentable over Connelly *et al.*, Negrier *et al.*, Uzan *et al.*, Hoeben *et al.*, Hao *et al.*, and further in view of Greenberg *et al.* (Blood (1998) Vol. 72, No. 6, pp. 1968-1977; referenced in IDS of Paper No. 4)." Office Action at page 9.

Applicants respectfully traverse. As set forth in M.P.E.P. § 2143.01, in order to establish a *prima facie* case of obviousness the Office must meet three criteria. "First, there must be some suggestion or incentive, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable

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expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (M.P.E.P. § 2143.01 and cases cited therein.)

As explained below, the Office has failed to establish a *prima facie* case of obviousness because the prior art cited by the Office does not give guidance or evidence that a skilled artisan would reasonably expect to succeed. One of ordinary skill would have no reasonable expectation of success in expressing Factor VIII in a hematopoietic cell type using the promoter characterized by Uzan if he were to combine the Factor VIII cDNA taught in Connelly and Negrier with the vectors taught in Hao. The addition of Greenberg does not cure this defect. Accordingly, the rejection of claims 1-3, 5-9, and 11 should be withdrawn.

Applicants believe that these references provide no reasonable expectation of success, because Hao merely speculates as to the possibility of targeting Factor IX expression to a specific lineage. (Hao; page 879, left column, second paragraph.) Moreover, there is no guidance as to what specific hematopoietic cell types should be targeted or whether any specific hematopoietic cell type would successfully express a different blood coagulation factor, Factor VIII. In fact, Hao states "[i]t is not known which specific hematopoietic cell type(s) would be best for expression of factor IX." *Id.* Further, Hao discloses in Figure 1 on page 875 that expression was high when the HL-60 cell line was induced to monocytoid differentiation, but low when induced to granulocytic differentiation. The production of only very low factor IX transcripts in

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granulocytes demonstrates that not all hematopoietic cells, even when transduced with the same vector, are capable of producing Factor IX, let alone Factor VIII. Thus, the vectors taught in Hao do not provide one of ordinary skill in the art with a reasonable expectation of success if they were to the use these vectors to express the modified Factor VIII cDNA as taught in Connelly and Negrier.

Hoeben attempted to evaluate the potential of the hematopoietic system as a target for Factor VIII expression. However, there was a failure to demonstrate "expression of factor VIII in vivo, either at the RNA or at the protein level." (Hoeben; page 341, summary.) This failure was particularly disappointing because Hoeben used retroviral vectors which, "because of their unequalled efficiency. . . . are the system of choice." (Hoeben; page 341, right column, third full paragraph.) Hoeben hypothesized that the lack of factor VIII expression was due to the vector's LTR promoter/enhancer. However, Hoeben then showed that the use of other vectors in which Factor VIII expression is driven by either the Herpes Simplex Virus Thymidine kinase gene promoter or the Simian Virus 40 (SV 40) promoter also resulted in undetectable quantities of Factor VIII secretion (Hoeben; page 344, right column, second paragraph.) Based on the failure of Hoeben to successfully express factor VIII in hematopoietic cells using a vector of "unequalled efficiency," one of skill in the art would not reasonably expect success.

Both Hoeben and Hao demonstrate that there is no reasonable expectation of successfully targeting the expression of Factor VIII to a hematopoietic cell type. Even if

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the GPIIb promoter taught in Uzan could be used to target expression of Factor VIII, there is no reasonable certainty that the targeted cell could successfully express Hao's DNA construct replaced with the modified cDNA of Connelly and Negrier. The Office has failed to establish a *prima facie* case of obviousness for at least the reasons stated above. Applicants respectfully submit that claims 1-3, 5-9, and 11 are not obvious and request that the rejection be withdrawn.

Nonstatutory Double Patenting Rejections

The Office provisionally rejected claim 11 under the doctrine of obviousness-type double patenting, stating that claim 11 is not patentably distinct over claim 13 of copending Application No. 09/559,344. Further, the Office provisionally rejected claims 1-3, 5-9, and 11 under the doctrine of obviousness-type double patenting, stating that the claims are not patentably distinct over claims 1-14 of copending Application No. 09/559,344 in view of Connelly *et al.* Finally, the Office provisionally rejected claims 1-3, 5-9, and 11 under the doctrine of obviouness type-double patenting, stating that the claims are not patentably distinct over claim 7 of copending Application No. 09/880,887 in view of Hao *et al.*, Hoeben *et al.*, and Uzan *et al.* or over claims 1, 3, and 5 of U.S. patent No. 6,271,025 in view of Hao *et al.*, Hoeben *et al.*, and Uzan *et al.*

Applicants will consider filing a terminal disclaimer to overcome this rejection once patentable subject matter has been indicated in this case. Until then, Applicants request that the Examiner hold the rejection in abeyance.

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Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: September 5, 2003

By: _____
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